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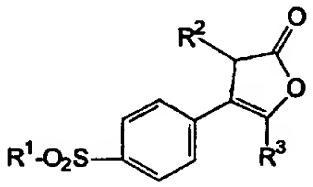

(I)

(57) Abstract

A 2-(3H)-oxazolone compound of formula (I), wherein: R^1 is an alkyl or amino group; R^2 is a naphthyl, unsubstituted phenyl or phenyl group, substituted by from 1 to 3 halogen atoms or alkyl, alkoxy or trifluoromethyl groups; and R^3 is hydrogen or an alkyl group.

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NEW 2-(3H)-OXAZOLONE DERIVATIVES

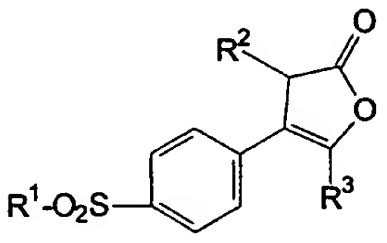
This invention relates to new therapeutically useful 2-(3H)-oxazolone derivatives, to processes for their preparation and to pharmaceutical compositions containing them.

The mechanism of action of non steroidal anti-inflammatory drugs is believed to be the inhibition of the enzyme cyclooxygenase (COX) and consequently, the conversion of arachidonic acid into prostaglandins. The identification of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes, led to the hypothesis that the selective inhibition of COX-2 would reduce inflammation without the side effects of classical non steroidal anti-inflammatory drugs, gastric and renal toxicity.

In accordance with this hypothesis, we have now found that certain 2-(3H)-oxazolone derivatives selectively inhibit COX-2 in preference to COX-1. These derivatives have efficacy and good tolerance in the treatment of COX-2 mediated diseases, such as inflammation, pain, fever and asthma, and fewer side effects, such as ulcerogenic activity.

Furthermore, we have found that when the 2-(3H)-oxazolone derivative is a 4-aminosulphonylphenyl-2-(3H)oxazolone derivative having an aryl moiety at the oxazolone 3-position the substitution pattern of the aryl moiety is effectual in determining both the activity and selectivity of the compound.

Accordingly the present invention provides a compound which is a 2-(3H)-oxazolone of formula (I):



(I)

wherein:

R^1 is an alkyl or amino group;

R^2 is a naphthyl, unsubstituted phenyl or phenyl group, substituted by from 1 to 3 halogen atoms (preferably chlorine, bromine or fluorine) or alkyl, alkoxy or trifluoromethyl groups, and

R^3 is hydrogen or an alkyl group.

The alkyl groups and moieties, such as in the alkoxy groups, mentioned in relation to the groups R^1 to R^3 are usually "lower" alkyl, that is containing up to 6 and particularly up to 4 carbon atoms, the hydrocarbon chain being branched or straight. A preferred alkyl group or moiety is methyl.

In compounds of the invention where R^2 is a substituted phenyl group the substituents may be in any position on the phenyl group. For example, a single substituent may be on position 2, 3 or 4, (the 5 and 6 positions being equivalent to the 2 and 3 positions); and 2 or more substituents may be on any combination of positions 2, 3, 4, 5 and 6.

Preferred compounds of formula (I) are those in which R^1 is NH_2 or a methyl group; R^2 is a phenyl group substituted by from 1 to 3 substituents which may be the same or different and are selected from chlorine, fluorine and bromine atoms and methyl, ethyl, isopropyl, n-propyl, t-butyl, methoxy and trifluoromethyl groups; and R^3 is hydrogen or methyl.

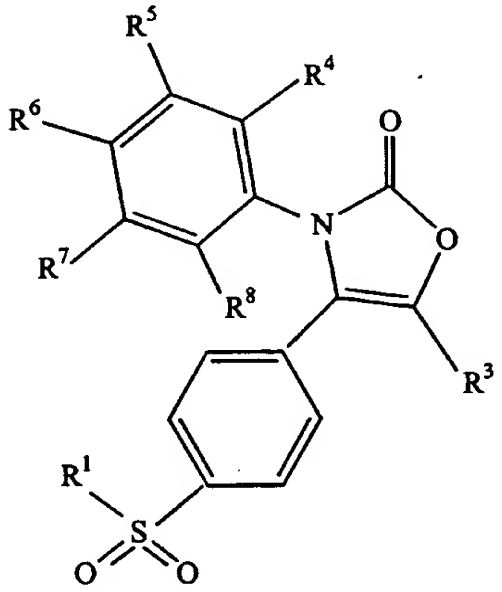
In compounds of formula (I) in which R^2 represents a phenyl group substituted by 2 or more substituents, the phenyl group is preferably substituted by at least 2 alkyl groups which may be the same or different, 1 alkyl group and 1 alkoxy group, 1 alkyl group and 1 halogen atom, 1 alkoxy group and 1 halogen atom, 2 halogen atoms which may be the same as or different or 1 trifluoromethyl group and 1 halogen atom. When R^2 represents a disubstituted phenyl group the substituents are preferably located at the 2 and 4, 2 and 5 or 3 and 4 positions.

In one group of preferred compounds of formula (I) R^2 is a phenyl group substituted by a methyl group, ethyl group, methoxy group or trifluoromethyl group at the 3 or 4 position and which is optionally further substituted at any of the remaining positions by one or more chlorine or fluorine atoms. Preferred compounds within this group are those wherein R^1 is NH_2 and R^3 is hydrogen or a methyl group, most preferably hydrogen.

In another group of preferred compounds of formula (I) R^2 is a difluoro phenyl group preferably a 2,5-difluoro diphenyl group or a 2,4-difluoro phenyl group.

In a further group of preferred compounds of formula (I) R^2 is a phenyl group substituted by one or two halogen atoms, preferably fluorine or chlorine, and R^3 is a methyl group.

Particularly preferred compounds of formula (I) are the compounds of formula:



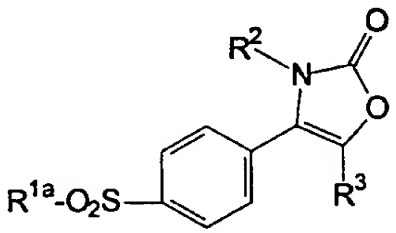
wherein the specific combination of values for each of R^1, R^3, R^4, R^5, R^6, R^7 and R^8 is as defined below:

R^1	R^3	R^4	R^5	R^6	R^7	R^8
Me	H	H	H	CH_3CH_2	H	H
Me	H	H	F	MeO	H	H
NH_2	H	H	Me	H	H	H
NH_2	H	Me	H	H	H	H
NH_2	H	H	H	Me	H	H
NH_2	H	H	H	H	H	H
NH_2	H	H	H	CH_3CH_2	H	H
NH_2	H	Cl	H	H	H	H
NH_2	H	H	H	Br	H	H
NH_2	H	H	H	MeO	H	H
NH_2	H	F	H	Me	H	H
NH_2	H	H	F	MeO	H	H
NH_2	H	H	Cl	MeO	H	H
NH_2	H	F	H	H	F	H
NH_2	H	H	F	Me	H	H
NH_2	H	H	Cl	Me	H	H
NH_2	H	H	F	F	H	H
NH_2	H	H	H	CF_3	H	H
NH_2	Me	H	H	H	H	H
NH_2	Me	H	H	F	H	H
NH_2	Me	F	H	H	H	H
NH_2	Me	H	H	Cl	H	H
NH_2	Me	H	Cl	Cl	H	H
NH_2	Me	H	H	Me	H	H
NH_2	Me	H	Me	H	H	H
NH_2	Me	H	F	Me	H	H
NH_2	Me	H	H	MeO	H	H
NH_2	Me	H	H	CF_3	H	H

Another preferred group of compounds of the invention are compounds according to formula (I) in which R^1 is NH_2; R^2 is a 1-naphthyl or 2-naphthyl group; and R^3 is hydrogen or methyl.

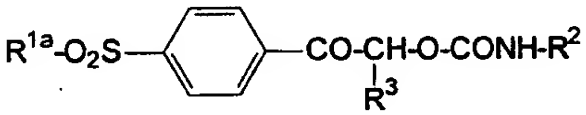
The present invention also provides processes for preparing a compound of formula (I) which depends on the definition of R^1.

The present invention provides a process for the preparation of a compound of formula (I) wherein R^1 is an alkyl group, viz. a 2-(3H)-oxazolone derivative of formula (II) :



(II)

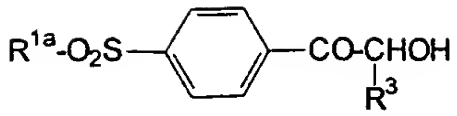
wherein R^{1a} is an alkyl group, and R^2 and R^3 are as defined above which comprises reacting a carbamate of formula (V):



(V)

wherein R^{1a}, R^2 and R^3 are as defined above with anhydrous acetic acid.

The carbamate of formula (V) may be obtained, for example, by reacting a phenacyl alcohol of formula (III):



(III)

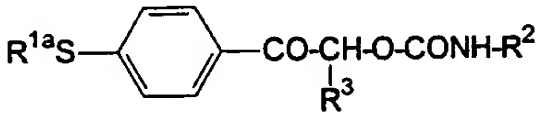
wherein R^{1a} and R^3 are as defined above, with an isocyanate of formula (IV):

$$OCN - R^2 \qquad (IV)$$

wherein R^2 is as defined above.

The reaction between the phenacyl alcohol of formula (III) and the isocyanate of formula (IV) may be carried out by heating a mixture of these two starting materials, optionally in the presence of an organic solvent such as toluene or xylene, at a temperature of from 80°C and 200°C.

The carbamate of formula (V) may also be prepared by reacting a thio derivative of general formula (VI):



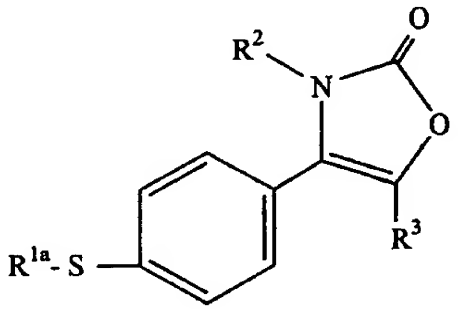
(VI)

wherein R^{1a}, R^2 and R^3 are as defined above, with an oxidizing agent, preferably magnesium monoperoxyphtalate or 3-chloroperoxybenzoic acid. The reaction is preferably carried out in an organic solvent such as a mixture of methylene chloride with methanol or ethanol, at a temperature of from 10°C to 40°C.

The carbamate of formula (V) may be isolated after each process by known methods. The carbamate may be heated to a temperature of from 80°C to 120°C with an excess of anhydrous

acetic acid to give the compound of formula (II).

The present invention also provides a process for the preparation of a compound of formula (I) wherein R^1 is an alkyl group, viz. a 2-(3H)-oxazolone derivative of formula (II), by reacting a mercapto derivative of formula (VII):

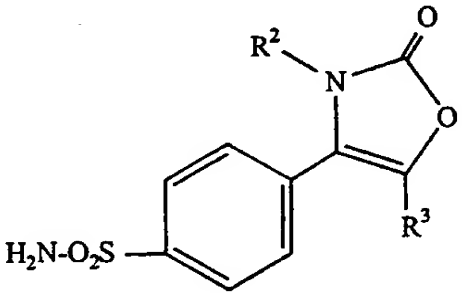


(VII)

wherein R^{1a}, R^2 and R^3 are as defined above, with an oxidizing agent, preferably with magnesium monoperoxyphtalate or 3-chloroperoxybenzoic acid.

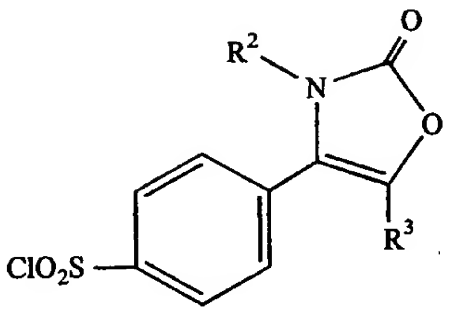
The reaction between the mercapto derivative of formula (VII) and the oxidizing agent is preferably carried out, as previously disclosed for the compound of formula (VI), in an organic solvent such as a mixture of methylene chloride with methanol or ethanol, at a temperature of from 10°C to 40°C.

The present invention additionally provides a process for the preparation of a compound of formula (I) wherein R^1 is an amino group, viz. the 2-(3H)-oxazolone derivative of formula (VIII):



(VIII)

wherein R^2 and R^3 are as defined above by reacting a chlorosulphonyl derivative of formula (IX):

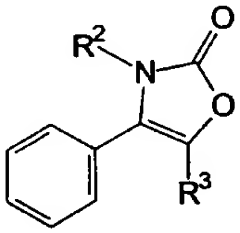


(IX)

wherein R^2 and R^3 are as defined above with ammonia.

This reaction is preferably carried out at a temperature of from 10°C to 40°C.

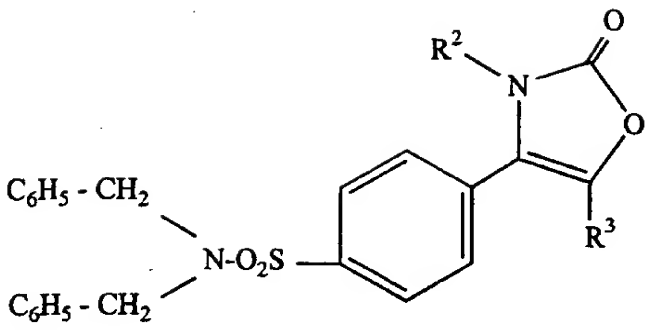
The chlorosulphonyl derivative of formula (IX) may, for example, be prepared by reacting a compound of formula (X):



(X)

wherein R^2 and R^3 are as defined above with chlorosulphonic acid, preferably at a temperature of from 80°C to 120°C.

The present invention further provides a process for the preparation of a compound of formula (I) wherein R^1 is an amino group viz, the 2-(3H)-oxazolone derivative of formula (VIII) by debenzylation of the corresponding compound of formula (XI):



(XI)

wherein R^2 and R^3 are as defined above.

The debenzylation is preferably carried out with an excess of trifluoroacetic, sulphuric or methanesulphonic acid at a temperature of from 0°C to 120°C.

The intermediates of formulae (III) and (VI) used in the preparation of the compounds of the invention may be prepared by methods disclosed in the literature, for example, in M.F. Saettone, J. Org. Chem. 31, p. 1959 (1966).

The intermediate compounds of formulae (VII) and (X) may be prepared by the same process disclosed for the preparation of compounds of formula (II), with the appropriate starting materials.

The following biological tests and data further illustrate this invention.

COX-1 and COX-2 activities in human whole blood

For the whole-cell COX-1 and COX-2 assays in human whole blood, stock solutions (10^{-2}M) of the compounds of formula (I) were dissolved in dimethylsulphoxide, and further dilutions were done with physiological serum. Compound vehicle, at concentrations employed, did not affect enzyme activities.

Fresh blood from healthy volunteers who had not taken any non-steroidal anti-inflammatory drugs for at least 7 days prior to blood extraction was collected in heparinized tubes

(20 units of heparin per ml). For the COX-1 activity determination, five hundred µl aliquots of blood were incubated with either 5 µl vehicle (dimethylsulphoxide) or 5 µl of a test compound for 1h at 37°C. Calcium ionophore A23187 (25 µM) was added 20 min before stopping the incubation. Plasma was separated by centrifugation (10 min at 13000 rpm) and kept at -30°C until TXB_2 levels were measured using an enzyme immunoassay kit (ELISA).The effect of the compounds were evaluated by incubating each compound at five to six different concentrations with triplicate determinations. IC_{50} values were obtained by non-linear regression using InPlot, GraphPad software on an IBM computer

For the COX-2 activity determination, five hundred µl aliquots of blood were incubated in the presence of LPS (10µg/ml) for 24 h at 37°C in order to induce the COX-2 expression (Patriagnani *et al.*, J. Pharm. Exper. Ther. 271; 1705-1712 (1994)). Plasma was separated by centrifugation (10 min at 13000 rpm) and kept at -30°C until PGE_2 levels were measured using an enzyme immunoassay kit (ELISA). The effects of inhibitors were studied by incubating each compound (5 µl aliquots) at five to six different concentrations with triplicate determinations in the presence of LPS for 24 hours. IC_{50} values were obtained by non-linear regression using InPlot, GraphPad software on an IBM computer.

Anti-inflammatory activity (adjuvant arthritis)

Male Wistar rats weighing 175-200 g with free access to food and water were used. On day 0, the animals received an intraplantar injection of a suspension of Mycobacterium tuberculosis in paraffin oil (0.5 mg/rat) on the left hind paw. A group of 8 nonarthritic control rats were injected with paraffin oil alone. On days 11 and 14 after induction of arthritis, the volume of the hind paw of each rat was measured using a water plehysmograph. Animals whose paw

volumes increased during that time were selected. Rats were distributed into groups of 8 having equal mean paw volumes and an approximately equal standard deviation.

Test compounds were administered p.o. once daily for 7 days (days 14-20). Nonarthritic and arthritic control rats received vehicle alone for 7 days. The hind paw volumes were measured 20h after the last dose (on day 21). The body weight was determined every second day.

The results are expressed as the percentage of inhibition of inflammation (paw volume) for each treatment group, considering both the arthritic and nonarthritic vehicle controls. The ANOVA test was used for statistical studies.

Ulcerogenic activity

Animals : Male Wistar rats (Interfauna, U.K., Ltd.) weighing about 150-175 g were used. Animals were maintained on a 12:12 hour light-dark cycle (lights on at 7:00 am) at room temperature (22±1°C). Food and water were allowed *ad libitum*.

Procedure : The compounds were administered by the oral route once a day for 4 consecutive days. The body weight of each rat was assessed every day before drug administration. The animals were anesthesized 24h after the last dosing and 1 ml of blood was extracted by cardiac puncture using heparin (10 U/ml) as anticoagulant. The percentage of hematocrit was measured. The intestines were removed, opened longitudinally and gently washed. The macroscopic severity of the intestinal eorsions was assessed using a parametric scale, evaluating the number of the perforated and non-perforated intestinal ulcers by means of a lesion index ranging from 0 to 3 (0:no ulcers, 1:>10 ulcers, 2:10-25 ulcers to 3:>25 ulcers). No gastric ulcers are observed using this protocol.

The treatments were randomized in each experiment. The results were compared with those obtained in the vehicle-

treated group using the ANOVA test.

Results

The results obtained from the biological assays are shown in Tables 1, 2 and 3.

TABLE 1

COX-1 and COX-2 Inhibition

COMPOUND (*)	COX-1 (μM) (**)	COX-2 (μM) (**)	Ratio COX-1 : COX-2
Indomethacin	0.19	0.22	0.86
1	42.4	0.7	60.6
6	24.4	2.4	10.2
3	6.6	0.51	12.9
10	>100	1.96	51
17	5.1	1.13	4.9
18	5.8	0.78	7.4
20	49	1.8	27.2
21	46	0.51	90.2

(*) See structures in Table 4.
Indomethacin is 1-(4-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid.

(**) Results expressed as IC_{50} values.

TABLE 2

Anti-inflammatory activity

Compound	% Inhibition (dose, mg/kg)
Indomethacin	64(1)
6	64(1)
3	57(1)
10	40(1)
17	58(1)
18	57(1)

TABLE 3

Ulcerogenic activity

Compound	Dose (mg/kg)	Lesion index		Hematocrit (%)
		PU	NPU	
vehicle		0	0	40.6±0.2
Indomethacin	10	3	3	22.6±0.8
6	100	0	0	42.5±0.5
3	100	0	0	40.0±0.6
17	100	0	0	39.8±0.4
18	100	0	0	41.1±0.3

PU: perforated ulcers, NPU: non-perforated ulcers.

As shown in Table 1, the compounds of formula (I) are selective and potent COX-2 inhibitors. We have found that the compounds of the invention are more effective in inhibiting COX-2 activity than they are inhibiting COX-1 activity, whereas the reference compound indomethacin is a equipotent as COX-2 and

COX-1 inhibitor.Accordingly the preferred compounds of formula (I) have a ratio of (COX-1 IC_{50})μM/(COX-2 IC_{50})μM of at least 3, preferably at least 4.5 and most preferably at least 10. Also the preferred compounds of formula (I) are potent COX-2 inhibitors having a COX-2 IC_{50} value of less than 5μM preferably less than 3μM and most preferably less than 2 μM. All IC_{50} values being measured according to the standard conditions detailed above. Due to their low COX-1 activity, the compounds of formula (I) present an important anti-inflammatory activity (see Table 2) and the benefit of significantly less harmful side effects than the non-steroidal anti-inflammatory drugs commonly used (e.g. gastrointestinal toxicity (see Table 3), renal side-effects, reduced effect on bleeding times and asthma induction in aspirin-sensitive subjects).

The present invention provides a compound of formula (I) for use in a method of treatment of the human or animal body by therapy, in particular for the treatment of pain, fever or inflammation, to inhibit prostanoid-induced smooth muscle contraction or for the prevention of colorectal cancer.

The present invention also provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment of pain, fever or inflammation, to inhibit prostanoid-induced smooth muscle contraction or for the prevention of colorectal cancer.

The compounds of formula (I) are useful for relief of pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhoea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, bursitis, tendinitis, injuries, following surgical and dental procedures and arthritis including rheumatoid arthritis, osteoarthritis, gouty arthritis, spondyloarthopathies, systemic lupus erythematosus and juvenile arthritis. They may also be used in the treatment of skin inflammation disorders such as psoriasis, eczema,

burning and dermatitis. In addition, such compounds may be used for the prevention of colorectal cancer.

The compounds of formula (I) will also inhibit prostanoid-induced smooth muscle contraction and therefore may be used in the treatment of dysmenorrhoea, premature labour, asthma and bronchitis.

The compounds of formula (I) can be used as alternative to conventional non-steroidal anti-inflammatory drugs, particularly where such non-steroidal anti-inflammatory drugs may be contra-indicated such as the treatment of patients with gastrointestinal disorders including peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis, Crohn's disease, inflammatory bowel syndrome and irritable bowl syndrome, gastrointestinal bleeding and coagulation disorders, kidney disease (e.g. impaired renal function), those prior to surgery or taking anticoagulants, and those susceptible to non-steroidal anti-inflammatory drugs induced asthma.

The compounds can further be used to treat inflammation in diseases such as vascular diseases, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anaemia, Hodgkin's disease, scleroderma, type I diabetes, myasthenia gravis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, hypersensitivity, conjunctivitis, gingivitis and myocardial ischaemia.

Compounds of the present invention are inhibitors of cyclooxygenase-2 enzyme and are thereby useful to treat the cyclooxygenase-2 mediated diseases enumerated above.

The present invention furthermore provides a pharmaceutical composition which comprises, as active ingredient, at least one 2-(3H)-oxazolone derivative of formula (I) and a pharmaceutically acceptable carrier or diluent. Preferably the compositions are in a form suitable for oral, topical, inhalation, rectal, transdermal, nasal or parenteral administration. The pharmaceutically-acceptable carriers or diluents which are admixed with the active compound or

compounds to form the compositions of this invention are well known *per se* and the actual excipients used depend *inter alia* on the intended method of administration of the compositions. Compositions of this invention are preferably adapted for administration *per os*.

In this case, the compositions for oral administration may take the form of tablets, capsules, lozenges or effervescent granules or liquid preparations such as elixirs, syrups or suspensions, all containing one or more compounds of the invention. Such preparations may be made by methods well known in the art, for instance by mixing the 2-(3H)-oxazolone derivative of formula (I) with the pharmaceutically acceptable carrier or diluent.

The diluents which may be used in the preparation of the compositions include those liquid and solid diluents which are compatible with the active ingredient, together with colouring or flavouring agents if desired. Tablets or capsules may conveniently contain between 10 and 500 mg and preferably from 15 to 100 mg of active ingredient. The compounds may also be incorporated into pellets coated with appropriate natural or synthetic polymers known in the art to produce sustained release characteristics or incorporated with polymers into tablet form to produce the same characteristics.

The liquid compositions adapted for oral use may be in the form of solutions, suspensions or aerosols. The solutions may be aqueous-alcoholic solutions of a 2-(3H)-oxazolone in association with, for example, sucrose or sorbitol to form a syrup. The suspensions may comprise an insoluble or microencapsulated form of an active compound of the invention in association with water and other acceptable solvents together with a suspending agent or flavouring agent.

Compositions for inahalation administration may be in the form of solutions, suspensions or micronized powder, contained in an appropriate inhaler.

Compositions for parenteral injection may be prepared in

the form of microemulsions or microsuspensions in water or an appropriate parenteral injection fluid.

In human therapy, the doses of the 2-(3H)-oxazolone derivatives depend on the desired effect and duration of the treatment; adult doses are generally between 15 mg and 500 mg per day. In general the physician will decide the posology taking into account the age and weight of the patient being treated.

The 2-(3H)-oxazolone derivatives of formula (I) may be used in a method of treatment of any of the above conditions which comprises administering to a subject in need of such treatment an effective amount of the derivative of formula (I).

The following Examples further illustrate the invention.

EXAMPLE 1

A solution of 4-methylsulfonylphenacyl alcohol (4.6 g; 21.5 mmoles), 4-ethylphenyl isocyanate (3.5 g; 23.6 mmoles) and pyridine (0.6 ml) in toluene (30 ml) was boiled under reflux for 2 hours. After cooling, the solvent was removed under reduced pressure, the resulting oil was solved in glacial acetic acid (25 ml) and then boiled under reflux for 5 hours. The solvent was removed in vacuo, the residue solved with ethyl acetate and the resulting solution washed with sodium bicarbonate saturated solution and then with water. After drying (Na_2SO_4) the solvent was removed in vacuo and the obtained solid purified by column chromatography with silica gel and n-hexane-ethyl acetate 1:1 as eluent. 3-(4-ethylphenyl)-4-(4-methylsulfonylphenyl)-2-(3H)-oxazolone (1.7 g) was obtained, m.p. 199°C (compound 1 in Table 4).

EXAMPLE 2

Example 1 was repeated except that 3-fluoro-4-methoxyphenyl isocyanate (2.9g, 17.6 mmol) was used in place of the 4-ethylphenyl isocyanate. 3-(3-fluoro-4-methoxyphenyl)-4-(4-methylsulfonylphenyl)-2-(3H)-oxazolone (0.8g) was obtained

and purified by column chromatography with silica gel, m.p. 151°C (compound 2 in Table 4).

EXAMPLE 3

a) A solution of 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(3-methylphenyl) carbamate (20 g; 37.8 mmoles) in anhydrous acetic acid (100 ml) was boiled under reflux for 6 hours. The solvent was removed under reduced pressure and the obtained solid was treated with diethyl ether. 3-(3-methylphenyl)-4-[4-N,N dibenzylaminosulfonyl)phenyl]-2-(3H)-oxazolone crystallized (16 g), m.p.160-162°C.

b) A solution of the above compound (16 g; 31.3 mmoles) in concentrated sulphuric acid (35 ml) was stirred at 20°C for 5 minutes. The reaction mixture was poured into iced-water, the precipitated solid extracted with ethyl acetate and washed with aqueous saturated solution of sodium bicarbonate and then with water. The organic solution was dried (Na_2SO_4), the solvent removed in vacuo and the obtained solid was passed through a chromatography column containing silica gel and methylene chloride-ethyl acetate-acetic acid 78:10:1 as eluent. 3-(3-methylphenyl)-4-(4-aminosulfonylphenyl)-2-(3H)-oxazolone (7.3g) was obtained, m.p. 192°C (compound 3 in Table 4).

Other 2-(3H)-oxazolone derivatives of formula (I) in Table 4 were prepared according to the processes disclosed in these Examples, but with the appropriate starting materials.

EXAMPLE 4

Example 3 was repeated except that 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(2-methylphenyl) carbamate (4.0g, 7.6 mmol) was used in place of the 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(3-methylphenyl) carbamate. 3-(2-methylphenyl)-4-(4-aminosulfonylphenyl)-2-(3H)-oxazolone (0.8g) was obtained and purified by column chromatography with silica gel, m.p. 99-101(d)°C (compound 4 in Table 4).

EXAMPLE 5

Example 3 was repeated except that 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(4-methylphenyl) carbamate (3.3g, 6.3 mmol) was used in place of the 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(3-methylphenyl) carbamate. 3-(4-methylphenyl)-4-(4-aminosulfonylphenyl)-2-(3H)-oxazolone (1.0g) was obtained and purified by column chromatography with silica gel, m.p. 225°C (compound 5 in Table 4).

EXAMPLE 6

Example 3 was repeated except that 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-phenyl carbamate (7.2g, 13.9 mmol) was used in place of the 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(3-methylphenyl) carbamate. 3-phenyl-4-(4-aminosulfonylphenyl)-2-(3H)-oxazolone (2.8g) was obtained and purified by column chromatography with silica gel, m.p. 208°C (compound 6 in Table 4).

EXAMPLE 7

Example 3 was repeated except that 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(4-ethylphenyl) carbamate (2.6g, 4.8 mmol) was used in place of the 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(3-methylphenyl) carbamate. 3-(4-ethylphenyl)-4-(4-aminosulfonylphenyl)-2-(3H)-oxazolone (250mg) was obtained and purified by column chromatography with silica gel, m.p. 199°C (compound 7 in Table 4).

EXAMPLE 8

Example 3 was repeated except that 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(2-chlorophenyl) carbamate (8.5g, 16.0 mmol) was used in place of the 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(3-methylphenyl) carbamate. 3-(2-chlorophenyl)-4-(4-aminosulfonylphenyl)-2-(3H)-oxazolone (2.0g) was obtained and purified by recrystallisation from ethyl acetate m.p. 169°C (compound 8 in Table 4).

EXAMPLE 9

Example 3 was repeated except that 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(4-bromophenyl) carbamate (12.4g, 20.9 mmol) was used in place of the 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(3-methylphenyl) carbamate. 3-(4-bromophenyl)-4-(4-aminosulfonylphenyl)-2-(3H)-oxazolone (3.8g) was obtained and purified by recrystallisation from ethyl acetate m.p. 226°C (compound 9 in Table 4).

EXAMPLE 10

Example 3 was repeated except that 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(4-trifluoromethylphenyl) carbamate (4.9g, 8.4 mmol) was used in place of the 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(3-methylphenyl) carbamate. 3-(4-trifluoromethylphenyl)-4-(4-aminosulfonylphenyl)-2-(3H)-oxazolone (1.7g) was obtained and purified by column chromatography with silica gel and n-hexane/ethyl acetate (2:1) as eluent m.p. 196°C (compound 10 in Table 4).

EXAMPLE 11

Example 3 was repeated except that 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(4-methoxyphenyl) carbamate (14.4g, 26.5 mmol) was used in place of the 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(3-methylphenyl) carbamate. 3-(4-methoxyphenyl)-4-(4-aminosulfonylphenyl)-2-(3H)-oxazolone (1.4g) was obtained and purified by column chromatography with silica gel and n-hexane/ethyl acetate (1:1) as eluent m.p. 196°C (compound 11 in Table 4).

EXAMPLE 12

Example 3 was repeated except that 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(2-fluoro-4-methylphenyl) carbamate (8.7g, 15.9 mmol) was used in place of the 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(3-methylphenyl) carbamate. 3-(2-fluoro-4-methylphenyl)-4-(4-aminosulfonylphenyl)-2-(3H)-

oxazolone (1.7g) was obtained and purified by column chromatography with silica gel and n-hexane/ethyl acetate (1:2) as eluent m.p. 173°C (compound 12 in Table 4).

EXAMPLE 13

Example 3 was repeated except that 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(3-fluoro-4-methylphenyl) carbamate (2.9g, 5.3 mmol) was used in place of the 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(3-methylphenyl) carbamate. 3-(3-fluoro-4-methylphenyl)-4-(4-aminosulfonylphenyl)-2-(3H)-oxazolone (480mg) was obtained and purified by column chromatography with silica gel, m.p. 166°C (compound 13 in Table 4).

EXAMPLE 14

Example 3 was repeated except that 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(3-chloro-4-methylphenyl) carbamate (5.6g 10.0 mmol) was used in place of the 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(3-methylphenyl) carbamate. 3-(3-chloro-4-methylphenyl)-4-(4-aminosulfonylphenyl)-2-(3H)-oxazolone (2.2g) was obtained and purified by column chromatography with silica gel, m.p. 92-95°C (compound 14 in Table 4).

EXAMPLE 15

Example 3 was repeated except that 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(3,4-difluorophenyl) carbamate (3.6g, 6.5 mmol) was used in place of the 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(3-methylphenyl) carbamate. 3-(3,4-difluorophenyl)-4-(4-aminosulfonylphenyl)-2-(3H)-oxazolone (4.2g) was obtained and purified by column chromatography with silica gel, m.p. 168°C (compound 15 in Table 4).

EXAMPLE 16

Example 3 was repeated except that 4-(N,N-

dibenzylaminosulfonyl)phenacyl-N-(2,5-difluorophenyl) carbamate (4.5g, 8.2 mmol) was used in place of the 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(3-methylphenyl) carbamate. 3-(2,5-difluorophenyl)-4-(4-aminosulfonylphenyl)-2-(3H)-oxazolone (1.3g) was obtained and purified by column chromatography with silica gel, m.p. 171°C (compound 16 in Table 4).

EXAMPLE 17

Example 3 was repeated except that 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(3-fluoro-4-methoxyphenyl) carbamate (10.8g, 19.2 mmol) was used in place of the 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(3-methylphenyl) carbamate. 3-(3-fluoro-4-methoxyphenyl)-4-(4-aminosulfonylphenyl)-2-(3H)-oxazolone (3.6g) was obtained and purified by column chromatography with silica gel, m.p. 184°C (compound 17 in Table 4).

EXAMPLE 18

Example 3 was repeated except that 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(3-chloro-4-methoxyphenyl) carbamate (8.8g, 15.2 mmoles) was used in place of the 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(3-methylphenyl) carbamate. 3-(3-chloro-4-methoxyphenyl)-4-(4-aminosulfonylphenyl)-2-(3H)-oxazolone (3.1g) was obtained and purified by column chromatography with silica gel and n-hexane/ethyl acetate (1:1) as eluent m.p. 194°C (compound 18 in Table 4).

EXAMPLE 19

Example 3 was repeated except that 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(2-naphthyl) carbamate (8.2g, 14.5 mmol) was used in place of the 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(3-methylphenyl) carbamate. 3-(2-naphthyl)-4-(4-aminosulfonylphenyl)-2-(3H)-oxazolone(1.8g) was obtained and purified by column chromatography with silica gel, m.p. 186°C (compound 19 in Table 4).

EXAMPLE 20

Example 3 was repeated except that 4-(N,N-dibenzylaminosulfonyl)2-methylphenacyl-N-phenyl carbamate (3.4g, 6.5 mmol) was used in place of the 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(3-methylphenyl) carbamate. 3-phenyl-4-(4-aminosulfonylphenyl)-5-methyl-2-(3H)-oxazolone (170mg) was obtained and purified by column chromatography with silica gel and n-hexane/ethyl acetate (1:1) as eluent m.p. 101°C (compound 20 in Table 4).

EXAMPLE 21

Example 3 was repeated except that 4-(N,N-dibenzylaminosulfonyl)-2-methylphenacyl-N-(2-fluorophenyl) carbamate (1.5g, 2.7 mmol) was used in place of the 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(3-methylphenyl) carbamate. 3-(2-fluorophenyl)-4-(4-aminosulfonylphenyl)-5-methyl-2-(3H)-oxazolone (480mg) was obtained and purified by column chromatography with silica gel and n-hexane/ethyl acetate (2:5) as eluent m.p. 110-113°C (compound 21 in Table 4).

EXAMPLE 22

Example 3 was repeated except that 4-(N,N-dibenzylaminosulfonyl)-2-methylphenacyl-N-(4-fluorophenyl) carbamate (3.1g, 5.6 mmol) was used in place of the 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(3-methylphenyl) carbamate. 3-(4-fluorophenyl)-4-(4-aminosulfonylphenyl)-5-methyl-2-(3H)-oxazolone (200mg) was obtained and purified by column chromatography with silica gel, m.p. 100-105°C (compound 22 in Table 4).

EXAMPLE 23

Example 3 was repeated except that 4-(N,N-dibenzylaminosulfonyl)2-methylphenacyl-N-(4-chlorophenyl) carbamate (2.5g, 4.4 mmol) was used in place of the 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(3-methylphenyl) carbamate. 3-

(4-chlorophenyl)-4-(4-aminosulfonylphenyl)-5-methyl-2-(3H)-oxazolone (360mg) was obtained and purified by column chromatography with silica gel, m.p. 223°C (compound 23 in Table 4).

EXAMPLE 24

Example 3 was repeated except that 4-(N,N-dibenzylaminosulfonyl)2-methylphenacyl-N-(4-trifluoromethylphenyl) carbamate (3.6g, 6.0 mmol) was used in place of the 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(3-methylphenyl) carbamate. 3-(4-trifluoromethylphenyl)-4-(4-aminosulfonylphenyl)-5-methyl-2-(3H)-oxazolone (140mg) was obtained and purified by column chromatography with silica gel and n-hexane/ethyl acetate (1:1) as eluent m.p. 91°C (compound 24 in Table 4).

EXAMPLE 25

Example 3 was repeated except that 4-(N,N-dibenzylaminosulfonyl)2-methylphenacyl-N-(3-methylphenyl) carbamate (6.4g, 11.8 mmol) was used in place of the 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(3-methylphenyl) carbamate. 3-(3-methylphenyl)-4-(4-aminosulfonylphenyl)-5-methyl-2-(3H)-oxazolone (850mg) was obtained and purified by column chromatography with silica gel, m.p. 165°C (compound 25 in Table 4).

EXAMPLE 26

Example 3 was repeated except that 4-(N,N-dibenzylaminosulfonyl)2-methylphenacyl-N-(4-methylphenyl) carbamate (1.2g, 2.2 mmol) was used in place of the 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(3-methylphenyl) carbamate. 3-(4-methylphenyl)-4-(4-aminosulfonylphenyl)-5-methyl-2-(3H)-oxazolone (370mg) was obtained and purified by column chromatography with silica gel, m.p. 103-104°C (compound 26 in Table 4).

EXAMPLE 27

Example 3 was repeated except that 4-(N,N-dibenzylaminosulfonyl)2-methylphenacyl-N-(4-methoxyphenyl) carbamate (3.0g, 5.4 mmol) was used in place of the 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(3-methylphenyl) carbamate. 3-(4-methoxyphenyl)-4-(4-aminosulfonylphenyl)-5-methyl-2-(3H)-oxazolone (580mg) was obtained and purified by column chromatography with silica gel, m.p. 210°C (compound 27 in Table 4).

EXAMPLE 28

Example 3 was repeated except that 4-(N,N-dibenzylaminosulfonyl)-2-methylphenacyl-N-(3,4-dichlorophenyl) carbamate (4.7g, 7.9 mmol) was used in place of the 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(3-methylphenyl) carbamate. 3-(3,4-dichlorophenyl)-4-(4-aminosulfonylphenyl)-5-methyl-2-(3H)-oxazolone (1.0g) was obtained and purified by column chromatography with silica gel, m.p. 132-136°C (compound 28 in Table 4).

EXAMPLE 29

Example 3 was repeated except that 4-(N,N-dibenzylaminosulfonyl)-2-methylphenacyl-N-(3-fluoro-4-methylphenyl) carbamate (5.6g, 10.0 mmol) was used in place of the 4-(N,N-dibenzylaminosulfonyl)phenacyl-N-(3-methylphenyl) carbamate. 3-(3-fluoro-4-methylphenyl)-4-(4-aminosulfonylphenyl)-5-methyl-2-(3H)-oxazolone (820mg) was obtained and purified by column chromatography with silica gel and n-hexane/ethyl acetate (1:1) as eluent m.p. 212°C (compound 29 in Table 4).

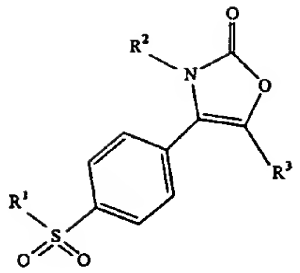


TABLE 4

Compound/ Example	R^1	R^2	R^3	Method of Example	m.p.°C
1	Me	$4CH_3CH_2-C_6H_4$	H	1	199
2	"	4MeO, 3F-C_6H_3	"	"	151
3	NH_2	$3Me-C_6H_4$	"	3	192
4	"	$2Me-C_6H_4$	"	"	99-101 (d)
5	"	$4-MeC_6H_4$	"	"	225
6	"	C_6H_5	"	"	208
7	"	$4CH_3CH_2-C_6H_4$	"	"	199
8	"	$2Cl-C_6H_4$	"	"	169
9	"	$4Br-C_6H_4$	"	"	226
10	"	$4CF_3-C_6H_4$	"	"	196
11	"	$4MeO-C_6H_4$	"	"	196
12	"	$4Me, 2F-C_6H_3$	"	"	173
13	"	$4Me, 3F-C_6H_3$	"	"	166
14	"	4Me, 3Cl-C_6H_3	"	"	92-95
15	"	$3, 4diF-C_6H_3$	"	"	168
16	"	$2, 5diF-C_6H_3$	"	"	171
17	"	4MeO, 3F-C_6H_3	"	"	184
18	"	4MeO, 3Cl-C_6H_3	"	"	194

Compound/ Example	R^1	R^2	R^3	Method of Example	m.p.°C
19	"	2-naphthyl	"	"	186
20	"	C_6H_5	Me	"	101
21	"	$2F-C_6H_4$	"	"	110-113
22	"	$4F-C_6H_4$	"	"	100-105
23	"	$4Cl-C_6H_4$	"	"	223
24	NH_2	$4CF_3-C_6H_4$	Me	3	91
25	"	$3Me-C_6H_4$	"	"	165
26	"	$4Me-C_6H_4$	"	"	103-104
27	"	$4MeO-C_6H_4$	"	"	210
28	"	3,4diCl-C_6H_3	"	"	132-136
29	"	$4Me,3F-C_6H_3$	"	"	212

EXAMPLE 30

15,000 Tablets each containing 50 mg of 3-(2-methylphenyl-4-(4-aminosulfonylphenyl)-2-(3H)-oxazolone (active ingredient) were prepared from the following formulation:

Active ingredient	750 g
Microcrystalline cellulose	585 g
Spray dried Lactose	2.985 g
Carboxymethyl starch	120 g
Sodium stearyl fumarate	30 g
Colloidal silicon dioxide	30 g

Procedure

All the powders were passed through a screen with an aperture of 0.6 mm, then mixed in a suitable mixer for 20 minutes and compressed into 300 mg tablets using 9 mm discs and flat bevelled punches. The disintegration time of the tablets was about 3 minutes.

EXAMPLE 31

100,000 capsules each containing 50 mg of 3-(4-ethylphenyl)-4-(4-aminosulfonylphenyl)-2-(3H)-oxazolone (active ingredient) were prepared from the following formulation:

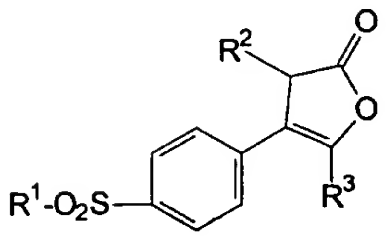
Active ingredient	5 kg
Lactose monohydrate	10 kg
Corn starch	1 kg
Magnesium stearate	0.2 kg
Colloidal silicon dioxide	0.1 kg

Procedure

The above ingredients were sieved through a 60-mesh sieve, and were loaded into a suitable mixer and filled into 100,000 gelatine capsules.

CLAIMS

1. A 2-(3H)-oxazolone compound of formula (I):



(I)

wherein:

R^1 is an alkyl or amino group;

R^2 is a naphthyl, unsubstituted phenyl or phenyl group substituted by from 1 to 3 halogen atoms or alkyl, alkoxy or trifluoromethyl groups; and

R^3 is hydrogen or an alkyl group.

2. A compound according to claim 1 in which R^1 is NH_2 or a methyl group; R^2 is a naphthyl group, unsubstituted phenyl group or phenyl group substituted by from 1 to 3 substituents which may be the same or different and are selected from chlorine, fluorine and bromine atoms and methyl, ethyl, isopropyl, n-propyl, t-butyl, methoxy and trifluoromethyl groups; and R^3 is hydrogen or a methyl group.

3. A compound according to claim 1 or 2 which R^2 is a phenyl group which is substituted by at least two substituents.

4. A compound according to claim 3 wherein the phenyl group is substituted by at least two alkyl groups which may be the same or different, one alkyl group and one alkoxy group, one alkyl group and one halogen atom, one alkoxy group and one halogen atom, two halogen atoms which may be the same or different or one trifluoromethyl group and one halogen atom.

5. A compound according to claim 3 or 4 wherein R^2 represents a disubstituted phenyl group substitued at the 2 and 4, 2 and 5 or 3 and 4 positions.

6. A compound according to any one of the preceding claims wherein R^2 is a phenyl group substituted by a methyl group, ethyl group, methoxy group or trifluoromethyl group at the 3 or 4 position and which is optionally further substituted at any of the remaining positions by one or more chlorine or fluorine atoms.

7. A compound according to claim 6 wherein R^2 is a phenyl group substituted by a methyl group, ethyl group or trifluoromethyl group.

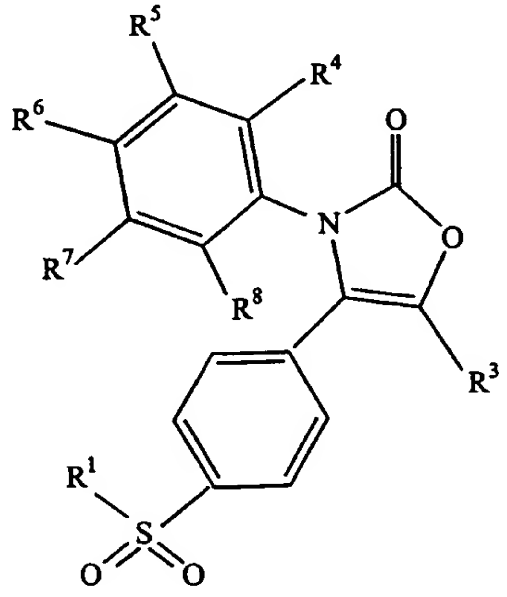
8. A compound according to claim 6 wherein R^2 is a phenyl group substituted by a methoxy group and one chlorine or fluorine atom.

9. A compound according to any one of claims 1 to 5 wherein R^2 is a difluorophenyl group.

10. A compound according to any one of claims 6 to 9 wherein R^1 is NH_2 and R^3 is hydrogen.

11. A compound according to any one of the claims 1 to 5 wherein R^1 is NH_2, R^2 is a phenyl group substituted by one or two fluorine or chlorine atoms and R^3 is a methyl group.

12. A compound according to any one of the preceding claims selected from the compounds of formula:



wherein the combination of values for each of R^1, R^3, R^4, R^5, R^6, R^7 and R^8 is as defined below:

R^1	R^3	R^4	R^5	R^6	R^7	R^8
Me	H	H	H	CH_3CH_2	H	H
Me	H	H	F	MeO	H	H
NH_2	H	H	H	H	H	H
NH_2	H	Me	H	H	H	H
NH_2	H	H	Me	H	H	H
NH_2	H	H	H	CH_3CH_2	H	H
NH_2	H	Cl	H	H	H	H
NH_2	H	H	H	Br	H	H
NH_2	H	H	H	MeO	H	H
NH_2	H	F	H	Me	H	H
NH_2	H	H	F	MeO	H	H
NH_2	H	H	Cl	MeO	H	H
NH_2	H	F	H	H	F	H
NH_2	H	H	F	Me	H	H
NH_2	H	H	Cl	Me	H	H
NH_2	H	H	F	F	H	H
NH_2	H	H	H	CF_3	H	H
NH_2	Me	H	H	H	H	H
NH_2	Me	H	H	F	H	H
NH_2	Me	F	H	H	H	H
NH_2	Me	H	H	Cl	H	H
NH_2	Me	H	Cl	Cl	H	H
NH_2	Me	H	H	Me	H	H
NH_2	Me	H	Me	H	H	H
NH_2	Me	H	F	Me	H	H
NH_2	Me	H	H	MeO	H	H
NH_2	Me	H	H	CF_3	H	H

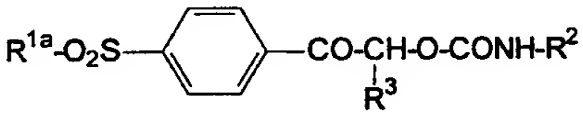
13. A compound according to claim 1 or 2 wherein R^2 is 1-naphthyl or 2-naphthyl.

14. A compound according to any one of the preceding claims which has a ratio of (COX-1 IC_{50})μM/(COX-2 IC_{50})μM of at least 3.

15. A compound according to any one of the preceding claims which has a COX-2 IC_{50} of less than 5μM.

16. A process for the preparation of a compound of formula (I) as defined in any one of the preceding claims which comprises:

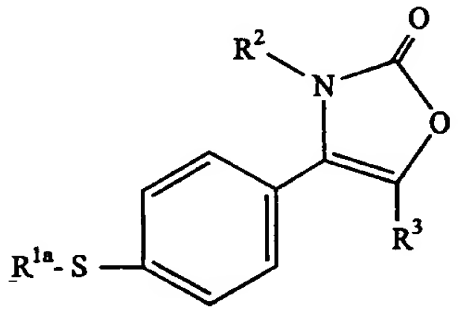
a) when R^1 is an alkyl group reacting a carbamate of formula (V):



(V)

wherein R^2 and R^3 are as defined in claim 1 and R^{1a} is an alkyl group, with anhydrous acetic acid;

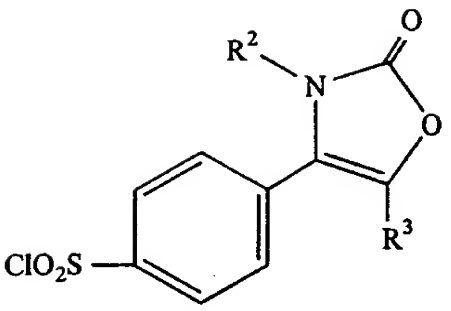
b) when R^1 is an alkyl group, reacting a mercapto derivative of formula (VII):



(VII)

wherein R^2 and R^3 are as defined in claim 1 and R^{1a} is an alkyl group with an oxidizing agent;

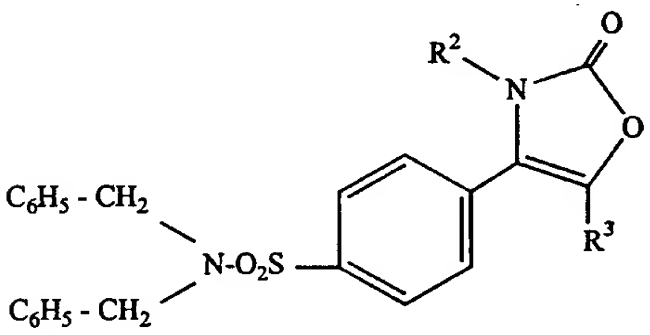
c) when R^1 is an amino group, reacting a chlorosulphonyl derivative of formula (IX):



(IX)

wherein R^2 and R^3 are as defined in claim 1 with ammonia; or

d) when R^1 is an amino group, debenzylating the corresponding compound of formula (XI):



(XI)

wherein R^2 and R^3 are as defined in claim 1.

17. A pharmaceutical composition which comprises, as active ingredient, at least one compound of formula (I) as defined in any one of claims 1 to 15 and a pharmaceutically acceptable carrier or diluent.

18. A compound of formula (I) as defined in any one of claims 1 to 15 or a composition as defined in claim 17 for use in a method of treatment of the human or animal body by therapy.

19. A compound of formula (I) as defined in any one of claims 1 to 15 or a composition as defined in claim 17 for use in the treatment of pain, fever or inflammation, to inhibit prostanoid-induced smooth muscle contraction or for the

prevention of colorectal cancer.

20. Use of a compound of formula (I) as defined in any one of claims 1 to 14 or a composition as defined in claim 17 in the manufacture of medicament for the treatment of pain, fever or inflammation, to inhibit prostanoid-induced smooth muscle contraction or for the prevention of colorectal cancer.

21. A method of treating pain, fever or inflammation, or of inhibiting prostanoid-induced smooth muscle contraction or of preventing colorectal cancer which comprises administering to a human or animal subject in need of such treatment, inhibition or prevention, a compound as defined in any one of claims 1 to 15 or a composition as defined in claim 17.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 98/05694

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D263/38 A61K31/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 27980 A (G.D.SEARLE & CO) 8 December 1994 see claims	1-21
P,X	WO 97 34882 A (GRUPO FARMACEUTICO ALMIRALL S.A.) 25 September 1997 see claims	1-21
P,X	WO 98 11080 A (LABORATOIRES UPSA) 19 March 1998 see claims	1-21

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 January 1999	15/01/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Henry, J

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Ir. ational application No.
PCT/EP 98/ 05694

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 21
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 21 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 98/05694

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9427980 A	08-12-1994	US 5380738 A	10-01-1995
		AU 6949594 A	20-12-1994
		EP 0699192 A	06-03-1996
		JP 8510736 T	12-11-1996
		US 5719163 A	17-02-1998
WO 9734882 A	25-09-1997	AU 2289397 A	10-10-1997
		EP 0888316 A	07-01-1999
WO 9811080 A	19-03-1998	FR 2753449 A	20-03-1998
		AU 4018897 A	02-04-1998